IQWiG Reports – Commission No. A21-101

Daratumumab (multiple myeloma) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Daratumumab (multiples Myelom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 October 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Hans Josef van Lier. IQWiG thanks the respondent for participating in the written exchange about how he experienced the disease and its treatment, and about treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IMWG	International Myeloma Working Group
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISS	International Staging System
PFS	progression-free survival
PT	preferred term
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-MY20	Quality of Life Questionnaire Myeloma Module 20
RCT	randomized controlled trial
R-ISS	Revised International Staging System
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug daratumumab in combination with pomalidomide and dexamethasone (daratumumab + pomalidomide + dexamethasone). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 27 July 2021.

Research question

The aim of this report is to assess the added benefit of daratumumab in combination with pomalidomide and dexamethasone (daratumumab + pomalidomide + dexamethasone) in comparison with the appropriate comparator therapy (ACT) in adult patients with multiple myeloma who had received 1 prior line of therapy with a proteasome inhibitor and lenalidomide and were refractory to lenalidomide or who received ≥ 2 prior lines of therapy including lenalidomide and a proteasome inhibitor and demonstrated disease progression on or after the most recent line of therapy.

The G-BA's specification of the ACT results in the research questions presented in Table 2.

Table 2: Research questions of the benefit assessment of daratumumab in combination with pomalidomide and dexamethasone

Research question	Therapeutic indication	ACT[a]
1	Adult patients with multiple myeloma who had received 1 prior line of therapy with a proteasome inhibitor and lenalidomide and were refractory to lenalidomide[b]	▪ Bortezomib in combination with pegylated liposomal doxorubicin or ▪ Bortezomib in combination with dexamethasone or ▪ Carfilzomib in combination with dexamethasone or ▪ Daratumumab in combination with bortezomib and dexamethasone
2	Adult patients with multiple myeloma who had received ≥ 2 prior lines of therapy including lenalidomide and a proteasome inhibitor and demonstrated disease progression on or after the most recent line of therapy[b]	▪ Bortezomib in combination with dexamethasone or ▪ Lenalidomide in combination with dexamethasone or ▪ **Pomalidomide in combination with dexamethasone (only for patients with disease progression <u>on</u> the most recent line of therapy)** or ▪ Elotuzumab in combination with lenalidomide and dexamethasone or ▪ Elotuzumab in combination with pomalidomide and dexamethasone (only for patients with disease progression <u>on</u> the most recent line of therapy) or ▪ Carfilzomib in combination with lenalidomide and dexamethasone or ▪ Carfilzomib in combination with dexamethasone or ▪ Daratumumab in combination with lenalidomide and dexamethasone or ▪ Daratumumab in combination with bortezomib and dexamethasone

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**.
b. High-dose chemotherapy with stem cell transplantation is assumed not to be an option for patients at the time of the current therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

To simplify presentation and improve readability, the running text of this benefit assessment uses the following designations for the research questions:

- Research question 1: Patients with 1 prior line of therapy
- Research question 2: Patients with ≥ 2 prior lines of therapy

For both research questions, the company departs from the G-BA's specification by using the respective ACTs from a consultation in 2020. All research questions of the present benefit assessment are answered in comparison with the ACT specified by the G-BA on 6 July 2021.

The company did not select an ACT for research question 1. For research question 2, the company selected pomalidomide in combination with dexamethasone. As per the approved therapeutic indication of pomalidomide + dexamethasone, this option is limited to patients with disease progression on the most recent line of therapy.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of added benefit.

Research question 1: Patients with 1 prior line of therapy

In its dossier, the company did not present any suitable data for assessing the added benefit of daratumumab + pomalidomide + dexamethasone in comparison with the ACT for adult patients with multiple myeloma who had received 1 prior line of therapy with a proteasome inhibitor and lenalidomide and were refractory to lenalidomide.

Research question 2: Patients with ≥ 2 prior lines of therapy

Study pool and study design

The APOLLO study was used for the benefit assessment. The APOLLO study is an ongoing, open-label RCT comparing daratumumab + pomalidomide + dexamethasone with pomalidomide + dexamethasone. It investigates adults with relapsed or refractory multiple myeloma who received 1 or more prior lines of therapy including both lenalidomide and a proteasome inhibitor. Patients had to demonstrate disease progression on or after the most recent line of therapy. Patients with disease progression on or up to 60 days after the most recent line of therapy were deemed to be progressing. In addition, patients had to have exhibited at least minimal response in at least 1 prior line of therapy.

Based on the treatment algorithm presented in the guidelines, patients without prior stem cell transplantation were presumably not indicated for high-dose chemotherapy with subsequent stem cell transplantation at study inclusion in the given therapeutic indication [1].

A total of 304 patients were randomized to treatment with daratumumab + dexamethasone (n = 151) or pomalidomide + dexamethasone (n = 153).

The use of daratumumab + pomalidomide + dexamethasone as well as of pomalidomide + dexamethasone was generally in line with the specifications of the Summaries of Product Characteristics (SPCs) for daratumumab and pomalidomide.

The primary outcome of the study was progression-free survival (PFS). As further patient-relevant outcomes, overall survival as well as outcomes from the morbidity, health-related quality of life, and adverse events (AEs) categories were surveyed.

For the APOLLO study, results on 2 data cut-offs were available at the time of the benefit assessment. Data cut-off 1 (21 July 2020) is a predefined primary analysis of all outcomes; the analysis had been planned to be performed after the occurrence of a total of 188 PFS events and actually took place after 190 PFS events. Data cut-off 2 (15 November 2020) is a 120-day safety data cut-off requested by the Food and Drug Administration (FDA) with analyses of only side effects outcomes.

This benefit assessment uses the results from data cut-off 1 for the outcomes of mortality, morbidity, and health-related quality of life and the results from data cut-off 2 for side effects outcomes.

Relevant subpopulation

For research question 2, the company used the subpopulation with ≥ 2 prior lines of therapy (135 patients in each study arm). This subpopulation includes patients with disease progression on or after the most recent line of therapy and therefore also contains patients who are not therapeutically indicated for pomalidomide + dexamethasone (i.e. patients who demonstrated disease progression after the most recent line of therapy). The company did not provide the percentage of patients from its operationalized subpopulation who experienced disease progression on the most recent line of therapy. However, based on data on the percentage of refractory patients, it is estimated to equal at least 78%. In the present situation, this is deemed a sufficient approximation of 80%. However, it would have been possible for the company to operationalize the relevant subpopulation, taking into account the limitations for the comparator therapy (pomalidomide + dexamethasone). In terms of certainty of results, the consequent uncertainty means that at most hints, e.g. of added benefit, can be derived.

Furthermore, the available APOLLO data can be used to draw conclusions only regarding patients with ≥ 2 prior lines of therapy whose disease progression occurred on the most recent line of therapy. No relevant data were available for patients whose progression occurred after the most recent line of therapy.

Risk of bias

The risk of bias across outcomes is rated as low for the APOLLO study. On the outcome level, the risk of bias is deemed high, except for the outcome of overall survival. In addition, due to the uncertainty regarding the operationalized subpopulation, the APOLLO study can be used to derive at most hints, e.g. for added benefit, for all outcomes.

Results

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment arms was found. Consequently, there is no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. An added benefit is therefore not proven for this outcome.

Morbidity

Symptoms

Symptoms outcomes were surveyed using the disease-specific instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire

Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire Myeloma Module 20 (QLQ-MY20). Time to deterioration by ≥ 10 points (scale range 0 to 100) was analysed.

No statistically significant difference between treatment arms was found for any of the symptoms outcomes of the EORTC QLQ-C30 (pain, fatigue, nausea and vomiting, dyspnoea, sleeplessness, appetite loss, constipation, diarrhoea) or EORTC QLQ-MY20 (disease symptoms and side effects of therapy). This results in no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone for any of them; an added benefit is therefore not proven.

Health status (European Quality of Life Questionnaire – 5 Dimensions [EQ-5D] visual analogue scale [VAS])

For the outcome of health status (EQ-5D VAS), time to deterioration by ≥ 15 points (scale range 0 to 100) was analysed. No statistically significant difference between treatment arms was found. This results in no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life outcomes were surveyed using the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-MY20. Time to deterioration by ≥ 10 points (scale range 0 to 100) was analysed for the individual functioning scales.

Global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning

For the outcomes of global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning, there is no statistically significant difference between treatment arms. This results in no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven.

Future perspective

For the outcome of future perspective, no statistically significant difference between treatment arms was found. However, there is an effect modification by age at baseline (< 65 years versus ≥ 65 years). For patients < 65 years at baseline, there is a hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. For patients ≥ 65 years of age at baseline, this results in no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven for these patients.

Body image

For the outcome of body image, no statistically significant difference between treatment arms was found. However, there is an effect modification by the attribute of sex (male versus female). For men, there is a hint of lesser benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. For women, there is no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added or lesser benefit is therefore not proven for women.

Side effects

No statistically significant difference between treatment arms was found for any of the outcomes of serious adverse events (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] ≥ grade 3), or discontinuation due to AEs. Consequently, none of them result in a hint of greater or lesser harm from daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; greater or lesser harm is therefore not proven for any of these outcomes.

Specific AEs

Leukopoenia (preferred term [PT], severe AEs) and pneumonia (PT, severe AEs)

For each of the specific AEs of leukopoenia (PT, severe AEs) and pneumonia (PT, severe AEs), there is a statistically significant difference to the disadvantage of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. Consequently, there is a hint of greater harm from daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone for each of them.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the presented results, the probability and extent of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with the ACT are assessed as follows:

Research question 1: Patients with 1 prior line of therapy

For answering research question 1, the company's dossier does not present any suitable data for assessing the added benefit of daratumumab + pomalidomide + dexamethasone in comparison with the ACT. For adult patients with multiple myeloma who had received 1 prior line of therapy with a proteasome inhibitor and lenalidomide and were refractory to

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [2,3].

lenalidomide, this results in no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: Patients with ≥ 2 prior lines of therapy

Regarding research question 2, the relevant subpopulation revealed, all in all, both 1 favourable and several unfavourable effects of daratumumab + pomalidomide + dexamethasone in comparison with the ACT, with some effects applying only to subgroups. For the side effects outcomes, unfavourable effects of daratumumab + pomalidomide + dexamethasone were found in comparison with the ACT only for the specific severe AEs of leukopoenia and pneumonia. In summary, for patients with multiple myeloma who had received ≥ 2 prior lines of therapy including lenalidomide and a proteasome inhibitor and who demonstrated disease progression on the most recent line of therapy, there is no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven. For this research question, no relevant data were available on patients whose disease progression occurred after the most recent line of therapy. No added benefit is therefore proven for these patients either.

Table 3 presents a summary of the probability and extent of added benefit of daratumumab.

Table 3: Daratumumab in combination with pomalidomide and dexamethasone – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	Adult patients with multiple myeloma who had received 1 prior line of therapy with a proteasome inhibitor and lenalidomide and were refractory to lenalidomide[b]	▪ Bortezomib in combination with pegylated liposomal doxorubicin or ▪ Bortezomib in combination with dexamethasone or ▪ Carfilzomib in combination with dexamethasone or ▪ Daratumumab in combination with bortezomib and dexamethasone	Added benefit not proven
2	Adult patients with multiple myeloma who had received ≥ 2 prior lines of therapy including lenalidomide and a proteasome inhibitor and demonstrated disease progression on or after the most recent line of therapy[b]	▪ Bortezomib in combination with dexamethasone or ▪ Lenalidomide in combination with dexamethasone or ▪ **Pomalidomide in combination with dexamethasone (only for patients with disease progression <u>on</u> the most recent line of therapy)** or ▪ Elotuzumab in combination with lenalidomide and dexamethasone or ▪ Elotuzumab in combination with pomalidomide and dexamethasone (only for patients with disease progression <u>on</u> the most recent line of therapy) or ▪ Carfilzomib in combination with lenalidomide and dexamethasone or ▪ Carfilzomib in combination with dexamethasone or ▪ Daratumumab in combination with lenalidomide and dexamethasone or ▪ Daratumumab in combination with bortezomib and dexamethasone	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**.
b. High-dose chemotherapy with stem cell transplantation is assumed not to be an option for patients at the time of the current therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of daratumumab in combination with pomalidomide and dexamethasone (daratumumab + pomalidomide + dexamethasone) in comparison with the ACT in adult patients with multiple myeloma who had received 1 prior line of therapy with a proteasome inhibitor and lenalidomide and were refractory to lenalidomide or who received ≥ 2 prior lines of therapy including lenalidomide and a proteasome inhibitor and demonstrated disease progression on or after the most recent line of therapy.

The G-BA's specification of the ACT results in the research questions presented in Table 4.

Table 4: Research questions of the benefit assessment of daratumumab in combination with pomalidomide and dexamethasone

Research question	Therapeutic indication	ACT[a]
1	Adult patients with multiple myeloma who had received 1 prior line of therapy with a proteasome inhibitor and lenalidomide and were refractory to lenalidomide[b]	▪ Bortezomib in combination with pegylated liposomal doxorubicin or ▪ Bortezomib in combination with dexamethasone or ▪ Carfilzomib in combination with dexamethasone or ▪ Daratumumab in combination with bortezomib and dexamethasone
2	Adult patients with multiple myeloma who had received ≥ 2 prior lines of therapy including lenalidomide and a proteasome inhibitor and demonstrated disease progression on or after the most recent line of therapy[b]	▪ Bortezomib in combination with dexamethasone or ▪ Lenalidomide in combination with dexamethasone or ▪ **Pomalidomide in combination with dexamethasone (only for patients with disease progression <u>on</u> the most recent line of therapy)** or ▪ Elotuzumab in combination with lenalidomide and dexamethasone or ▪ Elotuzumab in combination with pomalidomide and dexamethasone (only for patients with disease progression <u>on</u> the most recent line of therapy) or ▪ Carfilzomib in combination with lenalidomide and dexamethasone or ▪ Carfilzomib in combination with dexamethasone or ▪ Daratumumab in combination with lenalidomide and dexamethasone or ▪ Daratumumab in combination with bortezomib and dexamethasone

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**.
b. High-dose chemotherapy with stem cell transplantation is assumed not to be an option for patients at the time of the current therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

To simplify presentation and improve readability, the running text of this benefit assessment uses the following designations for the research questions:

- Research question 1: Patients with 1 prior line of therapy

- Research question 2: Patients with ≥ 2 prior lines of therapy

For both research questions, the company departs from the G-BA's specification by using the respective ACTs from a consultation in 2020. The latter were based on the preliminary therapeutic indication of daratumumab, which covers patients who demonstrated disease progression on the most recent line of therapy. In addition to these patients, however, the approved therapeutic indication of daratumumab in combination with pomalidomide and dexamethasone also covers patients who demonstrated disease progression occurring after the most recent line of therapy. On the basis of the approved therapeutic indication, therefore, the G-BA updated the ACT on 6 July 2021. All research questions of the present benefit assessment are answered in comparison with the ACT specified by the G-BA on 6 July 2021.

The company did not select an ACT for research question 1. For research question 2, the company selected pomalidomide in combination with dexamethasone. The approved therapeutic indication of pomalidomide + dexamethasone limits this option to patients with disease progression occurring on the most recent line of therapy (see Section 2.4.1.2.2).

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 Research question 1: Patients with 1 prior line of therapy

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources cited by the company in the dossier:

- Study list on daratumumab (as of 2 June 2021)
- Bibliographic literature search on daratumumab (most recent search on 2 June 2021)
- Search in trial registries / study results databases on daratumumab (most recent search on 6 July 2021)
- Search on the G-BA website on daratumumab (most recent search on 16 June 2021)

To check the completeness of the study pool:

- Search in trial registries for daratumumab (most recent search on 12 August 2021); see Appendix A of the full dossier assessment for search strategies.

In line with the company's findings, no relevant study was identified from the check.

In Module 4 B, Section 4.3.2.3 on further investigations, the company presents supplementary results of the APOLLO RCT's intervention arms for the subpopulation with 1 prior line of therapy as well as on the MM-014 cohort study. Both studies compared daratumumab +

pomalidomide + dexamethasone versus pomalidomide + dexamethasone. However, pomalidomide + dexamethasone is not an ACT option for research question 1 (patients with 1 prior line of therapy). For the APOLLO study, the company presents results of the subpopulation with 1 prior line of therapy. These patients had to have been refractory to lenalidomide (see Section 2.4.1.2 on the further description of the APOLLO study). To be included in the MM-014 study, patients treated with daratumumab + pomalidomide + dexamethasone had to have received 1 or 2 prior lines of therapy. The most recent line of therapy had to have been a lenalidomide-containing regimen with at least 2 consecutive cycles. For the MM-014 study, the company presents the results from the cohort of patients treated with daratumumab + pomalidomide + dexamethasone because the company did not conduct the study and has no access to analyses of the subpopulation with 1 prior line of therapy. A total of 63% of patients had received 1 prior line of therapy.

Given that a comparison with the ACT was missing, the company did in fact disregard the results of the APOLLO and MM-104 studies in the derivation of added benefit. This is appropriate.

2.3.2 Results on added benefit

In its dossier, the company did not present any suitable data for assessing the added benefit of daratumumab + pomalidomide + dexamethasone in comparison with the ACT for adult patients with multiple myeloma who had received 1 prior line of therapy with a proteasome inhibitor and lenalidomide and were refractory to lenalidomide. Consequently, there is no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

There is no proof of added benefit because the company did not present any suitable data for assessing the added benefit of daratumumab + pomalidomide + dexamethasone in comparison with the ACT for adult patients with multiple myeloma who had received 1 prior line of therapy with a proteasome inhibitor and lenalidomide and were refractory to lenalidomide.

This concurs with the company's assessment.

2.4 Research question 2: Patients with ≥ 2 prior lines of therapy

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources cited by the company in the dossier:

- Study list on daratumumab (as of 2 June 2021)
- Bibliographic literature search on daratumumab (most recent search on 2 June 2021)

- Search in trial registries / study results databases on daratumumab (most recent search on 6 July 2021)
- Search on the G-BA website on daratumumab (most recent search on 16 June 2021)

To check the completeness of the study pool:

- Search in trial registries for daratumumab (most recent search on 12 August 2021); see Appendix A of the full dossier assessment for search strategies.

The check did not identify any additional relevant studies.

2.4.1.1 Included studies

The study listed in the table below was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication[c] (yes/no [reference])
EMN14/54767414 MMY3013 (APOLLO[d])	Yes	Yes	No	Yes [4,5]	Yes [6,7]	Yes [8]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the tables below, the study will be referred to using this acronym.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool is consistent with that of the company.

2.4.1.2 Study characteristics

2.4.1.2.1 Study and intervention characteristics

Table 6 and Table 7 present the study used in the benefit assessment.

Table 6: Characterization of the included study – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
APOLLO	RCT, open-label, parallel-group	Adults with relapsed or refractory multiple myeloma with ▪ at least 1 prior line of therapy, including both lenalidomide and a PI ▪ disease progression on or after the most recent line of therapy[b] ▪ ECOG-PS ≤ 2	Daratumumab + pomalidomide + dexamethasone (N = 151) Pomalidomide + dexamethasone (N = 153) Analysed subpopulation[c] thereof: Daratumumab + pomalidomide + dexamethasone (n = 135) Pomalidomide + dexamethasone (n = 135)	Screening: up to 28 days Treatment: until disease progression[d], unacceptable toxicity, death, or study discontinuation Follow-up observation[e]: outcome-specific, at most until 5 years after randomization of the last patient	40 centres in Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Netherlands, Poland, Serbia, Spain, Turkey 06/2017–ongoing Data cut-off dates: 21/07/2020[f] 15/11/2020[g]	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Study participants who had received only 1 prior line of therapy had to exhibit disease progression on or within 60 days after completion of the lenalidomide-containing treatment regimen (lenalidomide refractory).
c. Patients with ≥ 2 prior lines of therapy.
d. Disease progression was determined on the basis of the IMWG criteria [9,10].
e. Outcome-specific information is provided in Table 8.
f. Primary analysis, planned to be conducted after 188 PFS events and actually carried out after 190 PFS events.
g. A 120-day safety data cut-off; corresponds to an FDA-requested safety update 4 months after data cut-off 1.

AE: adverse event; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; FDA: Food and Drug Administration; IMWG: International Myeloma Working Group; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; PI: proteasome inhibitor; RCT: randomized controlled trial

Table 7: Characterization of the intervention – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study	Intervention	Comparison
APOLoral LO	Daratumumab 16 mg/kg BW i.v. or 1800 mg s.c.[a] Cycles 1–2: weekly (Days 1, 8, 15, 22) Cycles 3–6: every 2 weeks (Days 1, 15) From cycle 7: every 4 weeks (Day 1) + Pomalidomide 4 mg p.o. All cycles: Days 1–21 + Dexamethasone 40 mg p.o. per week for patients < 75 years or 20 mg p.o. per week for patients ≥ 75 years (all cycles: Days 1, 8, 15, 22)[b] Duration of 1 treatment cycle: 28 days	 Pomalidomide 4 mg p.o. All cycles: Days 1–21 + Dexamethasone 40 mg p.o. per week for patients < 75 years or 20 mg p.o. per week for patients ≥ 75 years (all cycles: Days 1, 8, 15, 22) Duration of 1 treatment cycle: 28 days
	Dose modifications ▪ Daratumumab: no dose modification allowed; in case of infusion-related reactions, treatment interruption for up to 28 days; treatment discontinuation in the event of longer interruptions ▪ Pomalidomide: Treatment interruption possible in case of grade 2–3 skin rash. In case of neutropoenia, thrombocytopoenia, or other grade ≥ 3–4 AEs, dose modification or treatment interruption with reinitiation at a reduced dose (minimum of 1 mg); treatment discontinuation in case of grade 4 skin reactions or when no further reduction is possible. ▪ Dexamethasone: at certain toxicities, dose reduction to a minimum of 10 mg (or 8 mg in patients ≥ 75 years of age), treatment interruption, or treatment discontinuation.	
	Premedication before daratumumab ▪ Dexamethasone 20 mg i.v. or p.o., or equivalent dose of a long-acting corticoid ▪ Paracetamol 650–1000 mg i.v. or p.o. ▪ Antihistamine ▪ Leukotriene inhibitor (optional) **Treatment after daratumumab** For study participants at higher risk of respiratory complications: ▪ antihistamine ▪ short-acting β2 adrenergic receptor agonist such as salbutamol ▪ medication controlling pulmonary disease	–
	Permitted pretreatment ▪ At least 1 prior line of therapy, including both lenalidomide and a PI **Nonpermitted prior treatment** ▪ Monoclonal anti-CD38 antibodies ▪ Pomalidomide ▪ Treatment of multiple myeloma within 2 weeks or 5 treatment half-lives, whichever is longer, before randomization ▪ Allogeneic or autologous stem cell transplantation within 12 weeks before the 1st dose of the study drug	

Table 7: Characterization of the intervention – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Study	Intervention	Comparison
	Permitted concomitant treatment ▪ Antibiotic infection prevention recommended ▪ Prevention of herpes zoster reactivation recommended ▪ Thrombosis prevention recommended ▪ Bisphosphonates ▪ Treatment of tumour lysis syndrome ▪ Emergency medication for infusion-related reactions, such as paracetamol, antihistamines, corticosteroids, bronchodilators, vasopressors, diuretics **Nonpermitted concomitant treatment** ▪ Other antineoplastic therapies for treating multiple myeloma	
a. The APOLLO study protocol's 1st amendment dated 13 October 2017 changed the administration route of daratumumab from i.v. to s.c. Up to this amendment, a total of 7 patients received an i.v. formulation of daratumumab. After the amendment, 4 of these patients switched to the s.c. administration route. The remaining 3 patients had already discontinued the study medication before the 1st amendment. b. In daratumumab weeks, 20 mg dexamethasone was administered as part of the premedication before daratumumab. Patients who received a total dose of 40 mg dexamethasone self-administered the remaining 20 mg on the following day. CD38: cluster of differentiation 38; i.v.: intravenously; PI: proteasome inhibitor; p.o.: orally; RCT: randomized controlled trial; s.c.: subcutaneously		

The APOLLO study is an ongoing, open-label RCT comparing daratumumab + pomalidomide + dexamethasone with pomalidomide + dexamethasone. It investigates adults with relapsed or refractory multiple myeloma who received 1 or more prior lines of therapy including both lenalidomide and a proteasome inhibitor. Patients had to demonstrate disease progression on or after the most recent line of therapy. In addition, patients had to have exhibited at least minimal response as per modified International Myeloma Working Group (IMWG) criteria dated 2016 [10] to at least 1 prior therapy line (i.e. primary refractory disease was ruled out). Up to the study protocol's 1st amendment dated 13 October 2017, the 2011 IMWG criteria [9] were used for study inclusion. Study participants who had received only 1 prior line of therapy had to have become refractory on or within 60 days after completion of the lenalidomide-containing treatment regimen (lenalidomide refractory).

In the APOLLO study, the terms "refractory" and "relapsed" are defined in accordance the criteria of the International Myeloma Working Group [9] as follows:

- Refractory myeloma is defined as disease which is nonresponsive to therapy or progresses within 60 days of last therapy.
- Relapsed myeloma is defined as previously treated myeloma which progresses and requires the initiation of another therapy but does not meet criteria for refractory myeloma.

Inclusion criteria allowed patients with or without prior stem cell transplantation. Based on the treatment algorithm presented in the guidelines, patients without prior stem cell transplantation were presumably not indicated for high-dose chemotherapy with subsequent stem cell transplantation at study inclusion in the present therapeutic indication [1].

A total of 304 patients were randomized to treatment with daratumumab + dexamethasone (n = 151) or pomalidomide + dexamethasone (n = 153). Stratification factors were the number of prior lines of therapy (1 versus 2 to 3 versus ≥ 4) and International Staging System (ISS) stage (I versus II versus III).

In both study arms, treatment was administered in the form of cycles lasting up to 28 days until the occurrence of a reason for discontinuation (e.g. disease progression, unacceptable toxicity, or revocation of consent). After discontinuation of either daratumumab or pomalidomide + dexamethasone, treatment with the remaining drug component(s) can be continued. There are no restrictions regarding subsequent therapies after the end of the study medication (Table 11 shows an overview of subsequent anti-myeloma therapies).

The use of daratumumab + pomalidomide + dexamethasone and of pomalidomide + dexamethasone is generally in line with the SPCs for daratumumab and pomalidomide [11,12].

The primary outcome of the study is PFS. Other surveyed patient-relevant outcomes were overall survival as well as outcomes from the morbidity, health-related quality of life, and AE categories.

2.4.1.2.2 Relevant subpopulation of the APOLLO study

The APOLLO study included adult patients with relapsed or refractory multiple myeloma who had at least 1 previous line of therapy, including both lenalidomide and a proteasome inhibitor, and who exhibited disease progression on or after the most recent therapy.

For research question 2 of the present benefit assessment, only patients with ≥ 2 prior therapy lines are initially relevant.

The approved therapeutic indication of the APOLLO comparator, pomalidomide + dexamethasone, results in another limitation of the subpopulation relevant for the benefit assessment because pomalidomide + dexamethasone is approved only for the treatment of patients with disease progression occurring on (not after) the most recent line of therapy [12]. As described in Section 2.2, the ACT was modified in accordance with the approved therapeutic indication briefly before the dossier was submitted.

Module 4 B of the company's dossier provides analyses of the subpopulation with ≥ 2 prior lines of therapy (135 patients in each study arm) and uses this subpopulation for deriving added benefit. This subpopulation includes patients with disease progression on or after the most recent line of therapy and therefore also contains patients who are not therapeutically indicated for pomalidomide + dexamethasone (i.e. patients who demonstrated disease progression after

the most recent line of therapy). The company did not provide the percentage of patients from its operationalized subpopulation who experienced disease progression on the most recent line of therapy. However, based on the data provided on the percentage of refractory patients, it can be estimated to be at least 78% (Table 9). In the present situation, this is deemed a sufficient approximation of 80% [13]. Conversely, the company would generally have been able to operationalize the relevant subpopulation, taking into account the limitations for the comparator therapy (pomalidomide + dexamethasone). In terms of certainty of results, the ensuing uncertainty means that at most hints, e.g. of added benefit, can be derived.

Furthermore, available APOLLO data allow drawing conclusions only on a subset of the subpopulation relevant for research question 2 – patients with ≥ 2 prior lines of therapy and disease progression on the most recent line of therapy. No relevant data were available for patients with disease progression after the most recent line of therapy.

2.4.1.2.3 Data cut-off dates

APOLLO is an ongoing study whose recruitment has been completed.

APOLLO results from 2 data cut-offs were available at the time of the benefit assessment.

- Data cut-off 1 (21 July 2020) is a predefined primary analysis which was planned to be done after a total of 188 PFS events and was actually completed after 190 PFS events, with results on all outcomes.
- Data cut-off 2 (15 November 2020): 120-day safety data cut-off requested by the FDA; results on side effects outcomes

The final analysis of overall survival has not yet been completed for the APOLLO study and is planned after a total of 166 deaths have occurred or 5 years after randomization of the last patient, whichever is first. At the time of data cut-off 1, 87 events had occurred.

The present benefit assessment uses the results from data cut-off 1 for the outcomes of mortality, morbidity, and health-related quality of life and the results from data cut-off 2 for side effects outcomes because these data cut-offs cover the longest available follow-up observation in each case. This concurs with the company's approach. As per dossier template, it is permissible to use analyses from different data cut-offs, provided they fall within the same timeframe.

The available data on the overall population show that, by data cut-off 2, 54 of 151 patients (36%) had died in the intervention arm, and 64 of 153 patients (42%) in the comparator arm. When compared with data cut-off 1, an additional 6 deaths occurred in the intervention arm and 13 in the comparator arm, each based on the total population. The company did not submit a statistical analysis of the outcome of overall survival.

2.4.1.2.4 Planned treatment duration and follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

Study **Outcome category** **Outcome**	**Planned follow-up observation**
APOLLO	
Mortality	
Overall survival	Until death for any cause, a maximum of 5 years after inclusion of the last patient
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-MY20), health status (EQ-5D VAS)	Until disease progression
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-MY20)	Until disease progression
Side effects	
All outcomes of the side effects category	Up to 30 days after the last dose of the study drug

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-MY20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Myeloma Module 20; RCT: randomized controlled trial; VAS: visual analogue scale

The follow-up observation periods for the outcomes of morbidity, health-related quality of life, and side effects have been systematically shortened since, as shown in Table 8, they were surveyed only until disease progression or for the period of treatment with the study drug plus 30 days (also see Section 2.4.1.2.6). To be able to draw a reliable conclusion for the entire study period or until patient death, these outcomes, like overall survival, would have to be surveyed and analysed over the entire period.

2.4.1.2.5 Characterization of the relevant subpopulation

Table 9 shows the characteristics of the subpopulations with ≥ 2 previous lines of therapy in the included APOLLO study.

Table 9: Characterization of the study population – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone, relevant subpopulation (multipage table)

Study Characteristic Category	**Daratumumab + pomalidomide + dexamethasone N[a] = 135**	**Pomalidomide + dexamethasone N[a] = 135**
APOLLO		
Age [years], mean (SD)	65 (10)	67 (9)
Sex [f/m], %	52/48	53/47
Ancestry, n (%)		
White	119 (88)	120 (89)
Black or African American	1 (1)	0 (0)
Asian	1 (1)	1 (1)
Other	0 (0)	1 (1)
Unknown	14 (10)	13 (10)
ECOG-PS at randomization, n (%)		
0	80 (59)	66 (49)
≥ 1	55 (41)	69 (51)
ISS stage at baseline, n (%)		
I	59 (44)	58 (43)
II	45 (33)	47 (35)
III	31 (23)	30 (22)
R-ISS stage, n (%)		
I	24 (18)	20 (15)
II	65 (48)	80 (59)
III	18 (13)	12 (9)
Missing	28 (21)[b]	23 (17)[b]
Cytogenetic risk group, n (%)		
Standard risk	58 (43)	63 (47)
High risk[c]	36 (27)	30 (22)
Missing	41 (30)[b]	42 (31)[b]
Myeloma type based on immunofixation, n (%)		
IgG	75 (56)	76 (56)
IgA	29 (22)	25 (19)
IgM	0 (0)	0 (0)
IgD	1 (1)	2 (2)
Light chain	24 (18)	29 (22)
Kappa	12 (9)	20 (15)
Lambda	12 (9)	9 (7)
Biclonal	2 (2)	0 (0)
Negative immunofixation	4 (3)	3 (2)
Disease duration: period from initial diagnosis to randomization [years], mean (SD)	6 (4)	6 (4)

Table 9: Characterization of the study population – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone, relevant subpopulation (multipage table)

Study Characteristic Category	**Daratumumab + pomalidomide + dexamethasone N[a] = 135**	**Pomalidomide + dexamethasone N[a] = 135**
Number of prior lines of therapy, n (%)		
2–3	114 (84)	113 (84)
≥ 4	21 (16)	22 (16)
Prior lines of therapy, n (%)		
Alkyating agents	123 (91)	123 (91)
Anthracyclines	37 (27)	36 (27)
PI + IMiD	135 (100)	135 (100)
PI + IMiD + alkylating agents	123 (91)	123 (91)
Bortezomib + lenalidomide	130 (96)	131 (97)
Elotuzumab	8 (6)	6 (4)
Panobinostat	4 (3)	5 (4)
Bortezomib + lenalidomide + carfilzomib	31 (23)	39 (29)
Bortezomib + lenalidomide + carfilzomib + thalidomide	15 (11)	16 (12)
Refractory to prior lines of therapy, n (%)		
Of the most recent line of therapy	106 (79)[b]	105 (78)[b]
Lenalidomide in the most recent line of therapy	78 (58)[b]	72 (53)[b]
PI	66 (49)[b]	69 (51)[b]
IMiD	103 (76)[b]	104 (77)[b]
PI and IMiD	59 (44)[b]	59 (44)[b]
Treatment discontinuation, n (%)[d]		
Data cut-off 1	89 (60)[e, f]	117 (78)[e, f]
Data cut-off 2[g]	95 (64)[e, h]	127 (85)[e, h]
Study discontinuation, n (%)		
Data cut-off 1	56 (37)[e, i]	66 (43)[e, i]
Data cut-off 2[g]	ND	

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. IQWiG calculations.
c. Positive for del(17p), t(4;14), or t(14;16).
d. Presumably discontinuation of at least 1 drug component.
e. Data based on the APOLLO total population (daratumumab + pomalidomide + dexamethasone: N = 151; pomalidomide + dexamethasone: N = 153).
f. The most common reasons for treatment discontinuation by data cut-off 1 were disease progression (44% versus 58%), death (7% versus 5%), and noncompliance (3% versus 8%).
g. Data from the 120-day safety data cut-off, an update of tolerability analyses after 4 months as requested by the FDA.
h. The most common reasons for treatment discontinuation by data cut-off 2 were disease progression (48% versus 63%), death (7% versus 5%), and noncompliance (3% versus 9%).
i. The most common reasons for study discontinuation by data cut-off 1 were death (32% versus 33%) and revocation of consent (4% versus 9%).

Table 9: Characterization of the study population – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone, relevant subpopulation (multipage table)

Study Characteristic Category	Daratumumab + pomalidomide + dexamethasone N[a] = 135	Pomalidomide + dexamethasone N[a] = 135
ECOG-PS: Eastern Cooperative Oncology Group Performance Status; f: female; Ig: immunoglobulin; IMiD: immunomodulatory drug; ISS: International Staging System; m: male; n: number of patients in the category; N: number of randomized patients; PI: proteasome inhibitor; RCT: randomized controlled trial; R-ISS: Revised International Staging System; SD: standard deviation		

Patient characteristics are broadly comparable between study arms. The patients of the relevant subpopulation were 66 years on average, and they included slightly more women than men. At randomization, an average of 6 years had passed since the diagnosis of multiple myeloma. All patients had received prior treatment with an immunomodulatory agent and a proteasome inhibitor, and about 78% were refractory to the most recent therapy line. The treatment arms are comparable with regard to disease severity, provided the ISS stage is used for the operationalization, but according to the Revised International Staging System (R-ISS), the comparator arm had a slightly higher percentage of patients in stage II or III. In both treatment arms, however, no R-ISS data were available for more than 20% of patients.

2.4.1.2.6 Treatment and follow-up observation duration as well as subsequent therapies

Table 10 shows the median duration of patient treatment as well as the median duration of follow-up observation for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone, relevant subpopulation

Study **Duration of the study phase** **Outcome category**	**Daratumumab + pomalidomide + dexamethasone** **N[a] = 135**	**Pomalidomide + dexamethasone** **N[a] = 135**
APOLLO		
Data cut-off 1 (21 July 2020):		
Treatment duration [months]		
Median [min; max][b]	11.5 [ND]	6.5 [ND]
Follow-up duration [months]		
Overall survival		
Median [min; max]	17.2 [ND]	16.2 [ND]
Morbidity, health-related quality of life		
Median[c] [min; max]	ND	ND
Side effects		
Median[d] [min; max]	ND	ND
Data cut-off 2 (15 November 2020)[e]		
Treatment duration [months]		
Median [min; max]	11.5 [ND]	6.5 [ND]
Follow-up duration [months]		
Overall survival	No data available[f]	
Morbidity	No data available[g]	
Health-related quality of life	No data available[g]	
Side effects	ND[h]	

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Inverse Kaplan-Meier method.
c. The data provided by the company on median follow-up duration (12.2 months in the intervention arm and 7.5 months in the comparator arm) are based on the time to the last survey prior to subsequent therapy. It is unclear why the company disregarded preplanned surveys after the start of subsequent therapy in its calculation of follow-up durations.
d. The data provided by the company on median follow-up duration (12.5 months in the intervention arm and 7.5 months in the comparator arm) are based on the patients' individual treatment durations + 30 days. Therefore, these data represent merely approximations, not the medians of the actual follow-up durations.
e. Data from the 120-day safety data cut-off, an update of tolerability analyses after 4 months as requested by the FDA.
f. Based on the overall population, the available data show that by data cut-off 2, 54 of 151 patients (36%) in the intervention arm and 64 of 153 patients (42%) in the comparator arm had died. When compared with data cut-off 1, an additional 6 deaths occurred in the intervention arm and 13 in the comparator arm, each based on the total population. The company did not submit a statistical analysis regarding the outcome of overall survival.
g. For data cut-off 2, no results were analysed for this outcome category.
h. The dossier's Module 4 B states that the median follow-up duration at data cut-off 2 was 20.9 months (21.0 versus 20.2 months). Given that the study provided for follow-up for side effects only up to 30 days after the end of study treatment (see Table 8) and, in view of the median treatment duration by data cut-off 2 being much shorter and differing markedly between study arms, the reported follow-up duration can be assumed to refer to overall survival or progression-free survival rather than side effects.

max: maximum; min: minimum; N: number of patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

At both data cut-offs of the APOLLO study, the median treatment duration of the relevant subpopulation was almost twice as long in the intervention arm as in the comparator arm (11.5 months versus 6.5 months).

Regarding the follow-up duration for the relevant subpopulation, data on the outcome categories of mortality, morbidity, and health-related quality of life are available exclusively from data cut-off 1 (21 July 2020). By this data cut-off, the median follow-up duration for the outcome of overall survival is comparable in the two study arms.

The information provided by the company on median follow-up duration for the patient-reported outcomes (12.2 months in the intervention arm and 7.5 months in the comparator arm) are based on the time to the last survey prior to subsequent therapy. It is unclear why the company disregarded planned surveys after the start of subsequent therapy in its calculation of follow-up durations.

Module 4 B of the dossier reports the median follow-up observation duration at data cut-off 2 (15 November 2020) as 20.9 months (21.0 months versus 20.2 months). The study specified the follow-up observation for side effects to be carried out only for up to 30 days after the end of study treatment (see Table 8); in view of the median treatment duration at data cut-off 2 being much shorter and differing markedly between study arms, the reported follow-up duration for severe AEs (CTCAE grade ≥ 3) as well as SAEs presumably refers to overall survival or progression-free survival rather than side effects.

Table 11 shows the subsequent therapies the APOLLO total population received after discontinuing the study drug. No separate data are available for the relevant subpopulation. However, the relevant subpopulation makes up about 90% of the APOLLO total population, and consequently, its data are presented to serve as an approximation.

Table 11: Information on subsequent multiple myeloma therapies – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone, total population; data cut-off 1 (21 July 2020) (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Daratumumab + pomalidomide + dexamethasone N[a] = 149	**Pomalidomide + dexamethasone N[a] = 150)**
APOLLO		
Total	54 (36.2)	84 (56.0)
Antineoplastic agents	49 (32.9)	80 (53.3)
Other antineoplastic agents	37 (24.8)	69 (46.0)
Carfilzomib	21 (14.1)	27 (18.0)
Bortezomib	10 (6.7)	28 (18.7)
Daratumumab	4 (2.1)	50 (33.3)
Cisplatin	3 (2.0)	3 (2.0)
Ixazomib	3 (2.0)	3 (2.0)
Belantamab mafodotin	2 (1.3)	2 (1.3)
Other antineoplastic agents	2 (1.3)	0 (0)
Selinexor	1 (0.7)	0 (0)
Carboplatin	1 (0.7)	0 (0)
Isatuximab	1 (0.7)	3 (2.0)
Monoclonal antibodies	1 (0.7)	2 (1.3)
Panobinostat	1 (0.7)	0 (0)
Pembrolizumab	1 (0.7)	0 (0)
Ixazomib citrate	0 (0)	3 (2.0)
Alkylating agents	23 (15.4)	35 (23.3)
Cyclophosphamide	19 (12.8)	27 (18.0)
Melphalan	5 (3.4)	8 (5.3)
Bendamustine	3 (2.1)	0 (0)
Melphalan flufenamide	2 (1.3)	2 (1.3)
Cytotoxic antibiotics and related substances	9 (6.0)	5 (3.3)
Doxorubicin	6 (4.0)	5 (3.3)
Pegylated liposomal doxorubicin hydrochloride	2 (1.3)	0 (0)
Doxorubicin hydrochloride	1 (0.7)	0 (0)
Plant-derived alkaloids and other natural substances	5 (3.4)	4 (2.7)
Etoposid	4 (2.7)	4 (2.7)
Vincristine sulfate	1 (0.7)	0 (0)
Antimetabolites	1 (0.7)	0 (0)
Fludarabine	1 (0.7)	0 (0)
Antineoplastic agents	1 (0.7)	0 (0)
Experimental antineoplastic agents	1 (0.7)	0 (0)

Table 11: Information on subsequent multiple myeloma therapies – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone, total population; data cut-off 1 (21 July 2020) (multipage table)

Study	**Patients with subsequent therapy n (%)**	
Drug class **Drug**	**Daratumumab + pomalidomide + dexamethasone N[a] = 149**	**Pomalidomide + dexamethasone N[a] = 150)**
Corticosteroids for systemic use	46 (30.9)	78 (52.0)
Corticosteroids for systemic use, pure	46 (30.9)	78 (52.0)
Dexamethasone	42 (28.2)	68 (45.3)
Dexamethasone sodium phosphate	2 (1.3)	6 (4.0)
Prednisone	2 (1.3)	7 (4.7)
Methylprednisolone	1 (0.7)	0 (0)
Prednisolone	0 (0)	1 (0.7)
Immunosuppressants	23 (15.4)	34 (22.7)
Pomalidomide	9 (6.0)	18 (12.0)
Lenalidomide	8 (5.4)	14 (9.3)
Thalidomide	7 (4.7)	3 (2.0)
Iberdomide	2 (1.3)	1 (0.7)
Experimental active substance	10 (6.7)	1 (0.7)

a. Data are based on the safety population of the APOLLO total population (149 versus 150 patients).

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

After discontinuation of the study treatment, subsequent multiple myeloma therapies can be administered without restrictions. Information on subsequent therapies is provided only on the level of the active substance, not the treatment regimen. The percentage of patients from the APOLLO overall population who had ≥ 1 lines of subsequent multiple myeloma therapy is lower in the intervention arm than in the comparator arm (36.2% versus 56.0%). Regarding specific subsequent therapies, the largest differences between treatment arms were found for subsequent therapy with daratumumab (2.1% versus 33.3%). Additional common subsequent therapies for which larger differences were found are immunomodulatory agents such as lenalidomide (5.4% versus 9.3%) and pomalidomide (6.0% versus 12.0%) as well as cyclophosphamide (12.8% versus 18.0%) and dexamethasone (28.2% versus 45.3%).

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

Study	Adequate random sequence generation	Allocation concealment	Blinding		Results-independent reporting	Lack of other aspects	Risk of bias at study level
			Patients	Treatment providers			
APOLLO	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the APOLLO study. This concurs with the company's assessment.

Restrictions resulting from the open-label study design are described in Section 2.4.2.2 under risk of bias at outcome level.

Transferability of the study results to the German healthcare context

The company reports that the APOLLO study is conducted in European countries, including Germany, and that about 90% of included patients are of white descent. The company adds that, in terms of biodynamic or kinetic differences between the individual population groups involved or between individual countries and Germany, there was no evidence which would meaningfully impact study results. Further, the company notes that the included patients' prior therapies typically reflected the treatment pathways seen in the German healthcare system. Therefore, the company assumes the results to be generally transferable to the German healthcare context.

The company did not present any further information on the transferability of study results to the German healthcare context.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Symptoms surveyed using the European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) and the EORTC QLQ Multiple Myeloma 20 (EORTC QLQ-MY20)
  - Health status, surveyed with EQ-5D VAS
- Health-related quality of life
  - Surveyed with the EORTC QLQ-C30 and EORTC QLQ-MY20
- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Further specific AEs (SOC, PT), if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 B).

Table 13 shows the outcomes for which data were available.

Table 13: Matrix of outcomes – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-MY20)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-MY20)	SAEs	Severe AEs[a]	Discontinuation due to AEs[b]	Leukopoenia (PT, severe AEs[a])	Pneumonia (PT, severe AEs [a])
APOLLO	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Operationalized as CTCAE grade ≥ 3.
b. Discontinuation of at least 1 drug component.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-MY20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Myeloma Module 20; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Notes on outcomes and analyses

Morbidity

Symptomatic progression

In Module 4 B, the company submitted the analysis of an outcome it called "symptomatic progression". This outcome was defined post hoc as time from randomization until either death or occurrence of disease progression in temporal proximity to ≥ 1 symptom deemed by the company to be patient relevant. The list of myeloma-associated symptoms deemed by the company to be patient relevant includes both specific AEs and severe AEs (operationalized as CTCAE grade ≥ 3) as well as deterioration of symptoms by ≥ 10 points, surveyed with individual items of the questionnaires EORTC QLQ-C30 and EORTC QLQ-MY20. Disease progression meets the definition of PFS and was determined using IMWG criteria and hence using laboratory diagnostics [9,10]. Temporal proximity to disease progression was defined as a period of 30 days before and afterwards. For a progression event to be rated as symptomatic, either myeloma-associated AE or deterioration by ≥ 10 points of a symptom reported through the mentioned questionnaires must have occurred within this time period.

Symptomatic disease progression is generally patient relevant. However, the chosen operationalization of the outcome symptomatic progression is unsuitable for adequately surveying symptomatic disease progression. This outcome was defined post hoc; however, the company failed to justify the inclusion and exclusion of specific AEs, severe AEs, or items of

the presented list based on predefined criteria. The methods used to select the criteria were inadequately described. In addition, temporal proximity is insufficient evidence for a relationship, particularly given the fact that the operationalization submitted by the company allowed the events (progression event and occurrence of a symptom rated as patient relevant by the company) to occur within a relatively long time period of 60 days.

For these reasons, the outcome of symptomatic progression was disregarded for the assessment.

Symptoms, health status, and health-related quality of life

For EORTC QLQ-C30 and EORTC QLQ-MY20, the company's dossier provided responder analyses on the percentage of patients with a change by ≥ 10 points and by ≥ 15% of the scale range (each with a scale range of 0 to 100). As discussed in the IQWiG General Methods [13,14], a response criterion should be predefined to cover at least 15% of the range of an instrument's scale (for post hoc analyses, exactly 15% of the range of the scale) in order to reflect with sufficient certainty a change which is perceivable for patients. For EORTC QLQ-C30 and its supplementary modules, the analysis with the previously accepted response threshold of 10 points was viewed as a sufficient approximation to an analysis with a 15% threshold (15 points) and was used for the benefit assessment (for an explanation, see [15]). Irrespective of the above, for a transition period until the revised module templates for the dossier enter into force, primarily analyses with the previously accepted response threshold of 10 points were used for the EORTC QLQ-C30 and all additional EORTC modules (see FAQs from the G-BA [16]).

For the outcome of health status (EQ-5D VAS), the company's dossier presents responder analyses for time to a change by ≥ 7 points or ≥ 10 points, respectively (scale range 0 to 100). These were not used for the dossier assessment but presented as supplementary information in Appendix B of the full dossier assessment. Further, the company's dossier presented responder analyses with the response criterion of 15% of the scale range. They were used for deriving added benefit.

For the outcomes from EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D VAS, the company presented responder analyses with the following operationalizations:

- Time to deterioration
- Time to improvement

From among these operationalizations, time to deterioration was used.

Due to the course of disease to be expected in the present therapeutic indication and taking into account the distribution of absolute values of the scales at baseline, an analysis on the deterioration of health status is of primary relevance for the present benefit assessment.

The information provided by the company fails to show whether time to deterioration was understood as time to first deterioration or time to definitive deterioration. Presumably, however, it is time to first deterioration.

According to the statistical analysis plan, time to deterioration was predefined via a response criterion determined through distribution-based approaches. The plan included death due to progression as a deterioration. However, there is no evidence of death being included as a deterioration in Module 4 B's operationalization of deterioration by ≥ 10 points.

Side effect outcomes

For the outcome of discontinuation due to AEs, Module 4 B of the company's dossier presents both analyses of time to discontinuation of ≥ 1 drug component and analyses of time to discontinuation of all drug components. After discontinuation of 1 drug component, the study protocol allowed patients to continue treatment with the remaining drug components, but treatment with pomalidomide and dexamethasone was possible only in combination. Based on the available data (3 drug components in the intervention arm and 2 drug components in the comparator arm), an analysis of only the discontinuation of all drug components cannot be meaningfully interpreted. Irrespective of this, analyses of discontinuation of ≥ 1 drug component were preferable because each AE which leads to the discontinuation of any drug component is relevant. Consequently, the results of the analysis of time to discontinuation of ≥ 1 drug component are used for the benefit assessment.

2.4.2.2 Risk of bias

Table 14 presents the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias at study and outcome levels – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone

Study	Study level	Outcomes										
		Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-MY20)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-MY20)	SAEs	Severe AEs[a]	Discontinuation due to AEs[b]	Leukopoenia (PT, severe AEs[a])	Pneumonia (PT, severe AEs [a])
APOLLO	L	L	H[c, d]	H[c, d]	H[c, d]	H[c, d]	H[c, d]	H[e]	H[e]	H[f]	H[e]	H[e]

a. Operationalized as CTCAE grade ≥ 3.
b. Discontinuation of ≥ 1 drug component.
c. Lack of blinding with subjective recording of outcomes.
d. Strongly decreasing and widely differing questionnaire return rates.
e. Large difference in median treatment duration (and hence follow-up duration) between intervention arm (treatment duration 11.5 months) and control arm (treatment duration 6.5 months).
f. Lack of blinding in the presence of subjective decision on treatment discontinuation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-MY20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Myeloma Module 20; H: high; L: low; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event

The risk of bias is considered low for the results on the outcome of overall survival. This concurs with the company's rating.

For the results of the outcomes of symptoms, health status, and health-related quality of life, the risk of bias is rated as high due to the study's open-label design and the decreasing and widely differing return rates of the respective questionnaires. This likewise concurs with the company's assessment.

For side effects outcomes, the risk of bias of results was rated as high. For SAEs and severe AEs, this rating is due to the differing median follow-up durations and incomplete follow-up for potentially informative reasons (largely driven by discontinuation of follow-up after disease progression, see Table 10). For the outcome of discontinuation due to AEs, lack of blinding is the sole reason for the high risk of bias. The rating of severe AEs departs from that of the company, which concluded that these results had a low risk of bias.

Summary assessment of the certainty of results

In addition to the described risk of bias on the outcome level, the uncertainty regarding the operationalized subpopulation means that the APOLLO study can be used to derive at most hints, e.g. for added benefit, for all outcomes (see Section 2.4.1.2.2).

2.4.2.3 Results

Table 15 summarizes the results of the comparison of daratumumab + pomalidomide + dexamethasone with pomalidomide + dexamethasone in patients with multiple myeloma who had received ≥ 2 prior lines of therapy including lenalidomide and a proteasome inhibitor and demonstrated disease progression on or after the most recent line of therapy. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier.

Appendix C of the full dossier assessment presents results on common AEs, common SAEs, and common severe AEs (CTCAE grade ≥ 3) as well as all AEs leading to treatment discontinuation. Kaplan-Meier curves relating to the event-time analyses are found in Appendix D of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, AEs) – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone, relevant subpopulation (multipage table)

Study Outcome category Outcome	Daratumumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
APOLLO					
Mortality (data cut-off 1, 21/07/2020)					
Overall survival	135	NR [22.5; NC] 41 (30.4)	135	NR [18.0; NC] 46 (34.1)	0.84 [0.55; 1.29]; 0.432
Morbidity (data cut-off 1, 21/07/2020)					
Symptoms (EORTC QLQ-C30), time to deterioration[b]					
Pain	135	4.0 [2.8; 7.7] 79 (58.5)	135	3.6 [2.8; 4.7] 77 (57.0)	0.90 [0.65; 1.24]; 0.507
Fatigue	135	2.3 [1.9; 3.8] 94 (69.6)	135	2.1 [1.9; 3.2] 85 (63.0)	1.00 [0.73; 1.35]; 0.983
Nausea and vomiting	135	13.0 [5.6; NC] 60 (44.4)	135	8.0 [4.9; 10.2] 64 (47.4)	0.87 [0.61; 1.25]; 0.446
Dyspnoea	135	7.4 [3.7; 13.7] 66 (48.9)	135	5.6 [3.7; 7.5] 70 (51.9)	0.80 [0.56; 1.14]; 0.210
Sleeplessness	135	8.4 [3.9; NC] 63 (46.7)	135	7.4 [5.6; 13.2] 56 (41.5)	1.04 [0.72; 1.50]; 0.841
Appetite loss	135	9.2 [5.6; NC] 62 (45.9)	135	7.4 [4.8; 11.5] 68 (50.4)	0.81 [0.57; 1.15]; 0.246
Constipation	135	6.7 [4.7; 16.4] 64 (47.4)	135	5.2 [3.3; 8.6] 65 (48.1)	0.91 [0.64; 1.29]; 0.583
Diarrhoea	135	14.3 [6.5; 26.7] 59 (43.7)	135	6.5 [5.6; NC] 53 (39.3)	0.96 [0.65; 1.40]; 0.822
Symptoms (EORTC QLQ-MY20), time to deterioration[b]					
Symptoms of disease	135	8.1 [5.6; NC] 63 (46.7)	135	6.5 [3.9; 15.4] 62 (45.9)	0.86 [0.60; 1.24]; 0.432
Side effects of therapy	135	4.7 [2.9; 7.4] 76 (56.3)	135	3.9 [2.8; 5.6] 73 (54.1)	0.95 [0.68; 1.32]; 0.741
Health status (EQ-5D VAS, time to deterioration[c])	135	10.4 [4.7; 18.7] 65 (48.1)	135	7.4 [4.0; 15.0] 61 (45.2)	1.00 [0.70; 1.42]; 0.989

Table 15: Results (mortality, morbidity, health-related quality of life, AEs) – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone, relevant subpopulation (multipage table)

Study Outcome category Outcome	Daratumumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Health-related quality of life (data cut-off 1, 21/07/2020)					
EORTC QLQ-C30, time to deterioration[d]					
Global health status	135	4.4 [2.2; 10.7] 75 (55.6)	135	4.8 [3.2; 6.1] 81 (60.0)	0.91 [0.66; 1.25]; 0.551
Physical functioning	135	3.9 [2.8; 6.5] 85 (63.0)	135	4.7 [2.9; 6.7] 77 (57.0)	1.03 [0.75; 1.41]; 0.854
Role functioning	135	2.9 [1.9; 4.9] 86 (63.7)	135	3.2 [2.4; 5.1] 80 (59.3)	1.01 [0.74; 1.39]; 0.936
Emotional functioning	135	6.1 [4.7; 11.9] 71 (52.6)	135	4.0 [3.5; 7.2] 73 (54.1)	0.84 [0.60; 1.18]; 0.313
Cognitive functioning	135	4.4 [2.9; 6.1] 85 (63.0)	135	4.8 [2.8; 6.0] 76 (56.3)	0.99 [0.72; 1.36]; 0.938
Social functioning	135	3.2 [2.2; 5.8] 85 (63.0)	135	2.4 [1.9; 3.9] 84 (62.2)	0.87 [0.64; 1.19]; 0.392
EORTC QLQ-MY20, time to deterioration[d]					
Future perspective	135	5.2 [3.2; 12.3] 72 (53.3)	135	3.9 [2.9; 6.5] 74 (54.8)	0.92 [0.66; 1.28]; 0.615
Body image	135	5.8 [4.0; 13.6] 70 (51.9)	135	7.9 [4.8; NC] 56 (41.5)	1.22 [0.85; 1.75]; 0.277
Side effects (data cut-off 2, 15/11/2020)					
AEs (supplementary information)	133	0.3 [0.2; 0.3] 130 (97.7)	132	0.3 [0.1; 0.3] 129 (97.7)	–
SAEs	133	13.6 [8.0; 17.7] 69 (51.9)	132	14.9 [9.2; NC] 55 (41.7)	1.20 [0.84; 1.72]; 0.320
Severe AEs[e]	133	0.7 [0.5; 0.7] 117 (88.0)	132	0.7 [0.7; 0.9] 113 (85.6)	1.21 [0.93; 1.57]; 0.159
Discontinuation due to AEs (≥ 1 drug component)	133	NR 11 (8.3)	132	NR 5 (3.8)	1.81 [0.62; 5.27]; 0.274
Leukopoenia (PT, severe AEs[e])	133	NR 20 (15.0)	132	NR 7 (5.3)	2.97 [1.26; 7.03]; 0.013
Pneumonia (PT, severe AEs[e])	133	NR 21 (15.8)	132	NR 9 (6.8)	2.24 [1.02; 4.92]; 0.044

Table 15: Results (mortality, morbidity, health-related quality of life, AEs) – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone, relevant subpopulation (multipage table)

Study Outcome category Outcome	Daratumumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
a. HR (including 95% CI) and p-value calculated using Cox proportional hazards model with treatment as the only explanatory variable, stratified by number of prior lines of therapy (2–3 vs. ≥ 4) and ISS stage (I vs. II vs. III); p-value for overall survival calculated using log rank test, stratified by number of prior lines of therapy (2–3 vs. ≥ 4) and ISS stage (I vs. II vs. III). b. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). c. A score decrease by ≥ 15% of the scale range (0 to 100) from baseline is defined as a clinically relevant deterioration. d. A score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). e. Operationalized as CTCAE grade ≥ 3. CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-MY20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Myeloma Module 20; HR: hazard ratio; ISS: International Staging System; CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached ; RCT: randomized controlled trial; VAS: visual analogue scale				

Due to the high risk of bias, the available data can be used to derive at most an indication, e.g. of added benefit, for the outcome of overall survival, and at most hints for all other outcomes.

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment arms was found. Consequently, there is no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. An added benefit is therefore not proven for this outcome.

This concurs with the company's assessment.

Morbidity

For the outcomes of the morbidity category, the company did not derive added benefit for individual outcomes. Instead, it derived a hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison to pomalidomide + dexamethasone on the basis of the overall morbidity results. It drew this conclusion on the basis of the outcome of

symptomatic progression. This outcome was disregarded in the present benefit assessment (see Section 2.4.2.1 for the reasoning).

Symptoms

Symptoms outcomes were surveyed using the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-MY20. Time to deterioration by ≥ 10 points (scale range 0 to 100) was analysed.

Pain, fatigue, nausea and vomiting, dyspnoea, sleeplessness, appetite loss, constipation, diarrhoea, disease symptoms, and side effects of therapy

No statistically significant difference between treatment arms was found for any of the symptoms outcomes of the EORTC QLQ-C30 (pain, fatigue, nausea and vomiting, dyspnoea, sleeplessness, appetite loss, constipation, diarrhoea) or EORTC QLQ-MY20 (disease symptoms and side effects of therapy). This results in no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone for any of them; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For the outcome of health status (EQ-5D VAS), time to deterioration by ≥ 15 points (scale range 0 to 100) was analysed. No statistically significant difference between treatment arms was found. This results in no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life outcomes were surveyed using the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-MY20. Time to deterioration by ≥ 10 points (scale range 0 to 100) was analysed for the individual functioning scales.

Taking into account the responder analyses on the improvement and deterioration of health-related quality of life, overall, the company did not derive any added benefit for the outcome category.

Global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning

There is no statistically significant difference between treatment arms for the outcomes of health-related quality of life (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), which were surveyed using EORTC QLQ-C30. This results in no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven.

Future perspective

For the outcome of future perspective, no statistically significant difference between treatment arms was found. However, there is an effect modification by age at baseline (< 65 years versus ≥ 65 years). For patients < 65 years at baseline, there is a hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. For patients ≥ 65 years of age at baseline, this results in no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven for these patients.

This departs from the company's assessment, which disregarded the effect modification for the relevant subpopulation and did not derive added or lesser benefit from the results.

Body image

For the outcome of body image, no statistically significant difference between treatment arms was found. However, there is an effect modification by the attribute of sex (male versus female). For men, there is a hint of lesser benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone (see Section 2.4.2.4). For women, there is no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added or lesser benefit is therefore not proven for women.

This departs from the company's assessment, which disregarded the effect modification for the relevant subpopulation and did not derive added or lesser benefit from the results.

Side effects

As per study protocol, progression events of multiple myeloma were not surveyed as AEs. No information is available on the definition of progression events not surveyed.

For the outcomes of the side effects category, the company did not derive added benefit for individual outcomes. Instead, it concluded on the basis of the tolerability results overall that there is no proof of greater harm from daratumumab + pomalidomide + dexamethasone in comparison to pomalidomide + dexamethasone.

SAEs, severe AEs, and discontinuation due to AEs

No statistically significant difference between treatment arms was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs. Consequently, none of them result in a hint of greater or lesser harm from daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; greater or lesser harm is therefore not proven for any of these outcomes.

Specific AEs

Leukopoenia (PT, severe AEs) and pneumonia (PT, severe AEs)

For each of the specific AEs of leukopoenia (PT, severe AEs) and pneumonia (PTs, severe AEs), there is a statistically significant difference to the disadvantage of daratumumab +

pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. Consequently, there is a hint of greater harm from daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone for each of them.

2.4.2.4 Subgroups and other effect modifiers

For this benefit assessment, the following potential effect modifiers were taken into account:

- Sex (male versus female)
- Age (< 65 versus ≥ 65 years)
- ISS stage at baseline (I versus II versus III)

All subgroup characteristics used in the present benefit assessment had been predefined in the APOLLO study. However, the subgroup characteristic of ISS stage at baseline had been predefined only for outcomes of the mortality, morbidity and health-related quality of life categories, not for outcomes of the side effects category.

Interaction tests are performed whenever at least 10 patients per subgroup were included in the analysis. For binary data, there must also be 10 events in at least 1 subgroup.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

The subgroup results which meet these criteria are shown in Table 16.

Table 16: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone, relevant subpopulation

Study Outcome Characteristic Subgroup	Daratumumab + pomalidomide + dexamethasone		Pomalidomide + dexamethasone		Daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone	
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]	p-value[a]
APOLLO						
Health-related quality of life						
EORTC QLQ-MY20 future perspective, time to deterioration[b] (data cut-off 1, 21/07/2020)						
Age						
< 65 years	56	NR [4.3; NC] 22 (39.3)	47	3.1 [2.9; 5.1] 29 (61.7)	0.50 [0.28; 0.88]	0.016
≥ 65 years	79	3.9 [1.9; 5.9] 50 (63.3)	88	4.9 [2.8; 13.1] 45 (51.1)	1.17 [0.78; 1.75]	0.460
Total					Interaction:	0.019
EORTC QLQ-MY20 body image, time to deterioration[b] (data cut-off 1, 21/07/2020)						
Sex						
Male	70	4.8 [3.8; 10.6] 39 (55.7)	72	NR [5.6; NC] 23 (31.9)	1.79 [1.06; 3.00]	0.029
Female	65	5.9 [3.0; NC] 31 (47.7)	63	5.1 [3.2; 11.1] 33 (52.4)	0.81 [0.49; 1.33]	0.413
Total					Interaction:	0.032

a. Hazard ratio (including 95% CI and p-value) calculated using Cox proportional hazards model with treatment and treatment x subgroup as explanatory variables.
b. A score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-MY20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Myeloma Module 20; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial

Health-related quality of life

EORTC QLQ-MY20:

Future perspective

For the outcome of future perspective, there was an effect modification by the attribute of age. For patients < 65 years at baseline, there is a statistically significant difference in favour of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide +

dexamethasone. For patients < 65 years, this results in a hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone.

For patients ≥ 65 years at study start, in contrast, there was no statistically significant difference between treatment groups. For patients ≥ 65 years, this results in no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven for these patients.

This departs from the company's approach insofar as the company did present subgroup analyses but ignored them in the derivation of added benefit.

Body image

For the outcome of body image, there was an effect modification by the attribute of sex. For men, a statistically significant difference was found to the disadvantage of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone. For men, there is therefore a hint of lesser benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone.

For women, in contrast, no statistically significant difference between treatment groups was found. Consequently, for women, there is no hint of greater or lesser harm of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added or lesser benefit is therefore not proven for women.

This departs from the company's approach to the extent that the company did present subgroup analyses but ignored them in the derivation of added benefit.

2.4.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are presented below. The various outcome categories and the effect sizes have been taken into account. The methods used for this purpose are explained in the IQWiG General Methods [13].

The approach for deriving an overall conclusion on any added benefit by aggregating the conclusions reached at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of added benefit at outcome level

On the basis of the results presented in Section 2.4.2, the extent of the respective added benefit at outcome level was estimated (see Table 17).

Table 17: Extent of added benefit at outcome level: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone** **Median time to event (months)** **Effect estimator [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality (data cut-off 1, 21/07/2020)		
Overall survival	NR vs. NR HR: 0.84 [0.55; 1.29]; p = 0.432	Lesser/added benefit not proven
Morbidity (data cut-off 1, 21/07/2020)		
Symptoms		
EORTC QLQ-C30, deterioration by ≥ 10 points		
Pain	4.0 vs. 3.6 months HR: 0.90 [0.65; 1.24]; p = 0.507	Lesser/added benefit not proven
Fatigue	2.3 vs. 2.1 months HR: 1.00 [0.73; 1.35]; p = 0.983	Lesser/added benefit not proven
Nausea and vomiting	13.0 vs. 8.0 months HR: 0.87 [0.61; 1.25]; p = 0.446	Lesser/added benefit not proven
Dyspnoea	7.4 vs. 5.6 months HR: 0.80 [0.56; 1.14]; p = 0.210	Lesser/added benefit not proven
Sleeplessness	8.4 vs. 7.4 months HR: 1.04 [0.72; 1.50]; p = 0.841	Lesser/added benefit not proven
Appetite loss	9.2 vs. 7.4 months HR: 0.81 [0.57; 1.15]; p = 0.246	Lesser/added benefit not proven
Constipation	6.7 vs. 5.2 months HR: 0.91 [0.64; 1.29]; p = 0.583	Lesser/added benefit not proven
Diarrhoea	14.3 vs. 6.5 months HR: 0.96 [0.65; 1.40]; p = 0.822	Lesser/added benefit not proven
EORTC QLQ-MY20, deterioration by ≥ 10 points		
Symptoms of disease	8.1 vs. 6.5 months HR: 0.86 [0.60; 1.24]; p = 0.432	Lesser/added benefit not proven
Side effects of therapy	4.7 vs. 3.9 months HR: 0.95 [0.68; 1.32]; p = 0.741	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone** **Median time to event (months)** **Effect estimator [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Health status		
EQ-5D VAS, deterioration by ≥ 15 points	10.4 vs. 7.4 months HR: 1.00 [0.70; 1.42]; p = 0.989	Lesser/added benefit not proven
Health-related quality of life (data cut-off 1, 21/07/2020)		
EORTC QLQ-C30, deterioration by ≥ 10 points		
Global health status	4.4 vs. 4.8 months HR: 0.91 [0.66; 1.25]; p = 0.551	Lesser/added benefit not proven
Physical functioning	3.9 vs. 4.7 months HR: 1.03 [0.75; 1.41]; p = 0.854	Lesser/added benefit not proven
Role functioning	2.9 vs. 3.2 months HR: 1.01 [0.74; 1.39]; p = 0.936	Lesser/added benefit not proven
Emotional functioning	6.1 vs. 4.0 months HR: 0.84 [0.60; 1.18]; p = 0.313	Lesser/added benefit not proven
Cognitive functioning	4.4 vs. 4.8 months HR: 0.99 [0.72; 1.36]; p = 0.938	Lesser/added benefit not proven
Social functioning	3.2 vs. 2.4 months HR: 0.87 [0.64; 1.19]; p = 0.392	Lesser/added benefit not proven
EORTC QLQ-MY20, deterioration by ≥ 10 points		
Future perspective		
Age		
< 65 years	NR vs. 3.1 months HR: 0.50 [0.28; 0.88]; p = 0.016 Probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
≥ 65 years	3.9 vs. 4.9 months HR: 1.17 [0.78; 1.75]; p = 0.460	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Daratumumab + pomalidomide + dexamethasone vs. pomalidomide + dexamethasone** **Median time to event (months)** **Effect estimator [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Body image		
Sex Male	4.8 vs. NR months HR: 1.79 [1.06; 3.00]; HR: 0.56 [0.33; 0.94][c] p = 0.029 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Lesser benefit; extent: minor
Female	5.9 vs. 5.1 months HR: 0.81 [0.49; 1.33]; p = 0.413	Lesser/added benefit not proven
Side effects (data cut-off 2, 15/11/2020)		
SAEs	13.6 vs. 14.9 months HR: 1.20 [0.84; 1.72]; p = 0.320	Greater/lesser harm not proven
Severe AEs	0.7 vs. 0.7 months HR: 1.21 [0.93; 1.57]; p = 0.159	Greater/lesser harm not proven
Discontinuation due to AEs (≥ 1 drug component)	NR vs. NR HR: 1.81 [0.62; 5.27]; p = 0.274	Greater/lesser harm not proven
Leukopoenia (severe AEs)	NR vs. NR HR: 2.97 [1.26; 7.03]; HR: 0.34 [0.14; 0.79][c] p = 0.013 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm; extent: considerable
Pneumonia (severe AEs)	NR vs. NR HR: 2.24 [1.02; 4.92]; HR: 0.45 [0.20; 0.98][c] p = 0.044 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor

a. Probability is stated whenever a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits according to the upper limit of the confidence interval (CI_u).
c. IQWiG calculation, reversed direction of effect to enable use of limits to derive the extent of added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper confidence limit; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-MY20: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Myeloma Module 20; HR: hazard ratio; NR: not reached; SAE: serious adverse event

2.4.3.2 Overall conclusion on added benefit

Table 18 summarizes the results which were factored into the overall conclusion on the extent of added benefit.

Table 18: Favourable and unfavourable effects from the assessment of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone

Favourable effects	Unfavourable effects
Health-related quality of life ▪ Age (< 65 years) ▫ Future perspective Hint of added benefit – extent: considerable	Health-related quality of life ▪ Sex (men) ▫ Body image Hint of lesser benefit – extent: minor
–	Serious/severe side effects ▪ Severe AEs ▫ Specific AEs: - Leukopoenia Hint of greater harm – extent: considerable - Pneumonia Hint of greater harm – extent: minor
AEs: adverse events	

Overall, on the basis of the subpopulation relevant for research question 2, one favourable and several unfavourable effects of daratumumab + pomalidomide + dexamethasone were found in comparison with pomalidomide + dexamethasone, with some effects applying only to subgroups.

For the outcomes of health-related quality of life, there is a favourable effect for the subgroup of patients < 65 years of age (hint of considerable added benefit in EORTC QLQ-MY20 – functioning scales, future perspective) and an unfavourable effect for the subgroup of male patients (hint of lesser benefit of minor extent in EORTC QLQ-MY20 – functioning scales, body image).

For the side effects outcomes, unfavourable effects of daratumumab + pomalidomide + dexamethasone were found in comparison with pomalidomide + dexamethasone only for the specific severe AEs of leukopoenia and pneumonia.

In summary, for patients with multiple myeloma who had received ≥ 2 prior lines of therapy including lenalidomide and a proteasome inhibitor and who demonstrated disease progression on the most recent line of therapy, there is no hint of added benefit of daratumumab + pomalidomide + dexamethasone in comparison with pomalidomide + dexamethasone; an added benefit is therefore not proven. For this research question, no relevant data were available on patients whose disease progression occurred after the most recent line of therapy. No added benefit is therefore proven for these patients either.

The assessment described above deviates from that by the company, which derived a hint of non-quantifiable added benefit for the entire research question.

2.5 Probability and extent of added benefit – summary

Table 19 presents a summary of the results of the benefit assessment of daratumumab + pomalidomide + dexamethasone in comparison with the ACT.

Table 19: Daratumumab in combination with pomalidomide and dexamethasone – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT**[a]	**Probability and extent of added benefit**
1	Adult patients with multiple myeloma who had received 1 prior line of therapy with a proteasome inhibitor and lenalidomide and were refractory to lenalidomide[b]	▪ Bortezomib in combination with pegylated liposomal doxorubicin or ▪ Bortezomib in combination with dexamethasone or ▪ Carfilzomib in combination with dexamethasone or ▪ Daratumumab in combination with bortezomib and dexamethasone	Added benefit not proven
2	Adult patients with multiple myeloma who had received ≥ 2 prior lines of therapy including lenalidomide and a proteasome inhibitor and demonstrated disease progression on or after the most recent line of therapy[b]	▪ Bortezomib in combination with dexamethasone or ▪ Lenalidomide in combination with dexamethasone or ▪ **Pomalidomide in combination with dexamethasone (only for patients with disease progression <u>on</u> the most recent line of therapy)** or ▪ Elotuzumab in combination with lenalidomide and dexamethasone or ▪ Elotuzumab in combination with pomalidomide and dexamethasone (only for patients with disease progression <u>on</u> the most recent line of therapy) or ▪ Carfilzomib in combination with lenalidomide and dexamethasone or ▪ Carfilzomib in combination with dexamethasone or ▪ Daratumumab in combination with lenalidomide and dexamethasone or ▪ Daratumumab in combination with bortezomib and dexamethasone	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**.
b. High-dose chemotherapy with stem cell transplantation is assumed not to be an option for patients at the time of the current therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Supplementary note on the ACT

After the dossier had been submitted, the G-BA modified the ACT again on 8 August 2021. This modification includes a new, additional treatment option for research question 2 (bortezomib in combination with liposomal pegylated doxorubicin). The present benefit assessment is based on the ACT specified on 6 July 2021. Implementation of the modified ACT would not affect the relevance of the data used in this benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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